REMARKS

Claims 1-19, 25-32, 53, 54, 61 and 64 are being examined and have been rejected.

Specification

The specification has been amended to recite the term "vitaxin" in capital letters and with an indication of trademark status wherever this occurs.

Rejection Under 35 U.S.C. 112, ¶1

Claim 54 was rejected under 35 U.S.C. 112, paragraph 1, on grounds that the specification is enabling for a protein composition but does not enable a vaccine. In response, this claim has been canceled.

Claims 1-19, 25-32, 53, 54, 61 and 64 were rejected under 35 U.S.C. 112, paragraph 1, on grounds that the specification is enabling for an isolated protein construct but does not reasonably provide enablement for all possible active fragments thereof.

In response, Applicants have amended claim 1 to recite this feature of an active fragment. In support thereof, Applicants direct the Examiner's attention to the application, at page 7, lines 10-14, where it is taught that the present invention relates to a protein construct wherein the pilus protein portion that is linked to an effector portion is a structurally stabilized pilus protein portion that comprises either a structurally-stabilized pilus protein or a structurally-stabilized fragment of such structurally-stabilized

pilus protein. At page 7, lines 26-27, where it states that active fragments commonly comprise all or part of the stabilizing donor strand. Thus, an active fragment is a fragment of a pilus protein that is structurally stabilized by comprising the donor strand.

Rejection Under 35 U.S.C. 112, ¶2

Claims 1-19, 25-32, 53, 54, 61 and 64 were rejected under 35 U.S.C. 112, paragraph 2, as being indefinite for use of the phrase "active fragments thereof" and for use of the phrase "effector portion."

In response, Applicants reiterate their above-arguments regarding use of active fragments. Such fragments are structurally-stabilized fragments of a pilin, thus pilin fragments containing a donor strand. Applicants believe that the specification makes this clear.

As to the term "effector portion" this is the part of the isolated protein construct that represents the effector, which could be an antibody or chemotherapeutic agent, which were elected from Applicant in response to the earlier restriction requirement.

Applicants have also amended claim 1 to recite "effector" in place of "effector portion" and direct the Examiner's attention to the application at page 6, lines 12-16., where it is stated that the dsc-subunits are linked to effector molecules, such as polypeptides, including antibodies, thereby providing highly useful therapeutic agents. Further support is found at page 11, lines 17-25, and in Figure 4, where different types of effectors are described, and at page 15, line 17, to page 16, line 2, where methods of preparing the protein constructs are described, and at page 21, lines 27-30 and page 22, lines 17-31, where different types of effector are described. Applicants believe that the application makes sufficiently clear what an effector, or effector portion, is.

Claims 2 and 10 were rejected under 35 U.S.C. 112, paragraph 2, for lack of antecedent basis for the term "usher-chaperone pathway."

In response, Applicants believe that the Examiner means claims 2 and 16, since claim 10 does not recite this phrase.

Applicants also direct the Examiner's attention to the application at page 16, lines 18-25, where the usher-chaperone pathway is described. The dependent claims 2 and 16 require no antecedent basis for this term in the parent claims because they merely recite that the pilus protein is limited to a pilus protein used to assemble pili via the usher-chaperone pathway, as opposed to pilus proteins not assembled by that pathway. Thus, the phrase "usher-chaperone pathway" merely serves to limit the pilus proteins that can form part of the claimed isolated protein construct. This would seem to be clear.

Claim 61 was rejected under 35 U.S.C. 112, paragraph 2, for lack of antecedent basis for the claim dependency from claim 59, in that claim 61 is drawn to a process whereas claim 59 is drawn to a protein construct. In response, claim 61 has been amended to recite "protein construct" in place of "process."

Claim 64 was rejected under 35 U.S.C. 112, paragraph 2, for use of the term vitaxin. In response, this claim has been amended to capitalize this word and make clear that it is a trademark.

Rejection Under 35 U.S.C. 102

Claims 1-5, 7-9 and 25-32 were rejected under 35 U.S.C. 102(b), as being anticipated by Jones et al (1993).

In response, Applicants note that the Office Action simply cites to Jones as disclosing an isolated protein construct comprising a pilus protein containing a pilin and an immunoglobulin and antibodies. This is not the invention of the claim.

It is established Patent Law that "Under 35 U.S.C. §102, anticipation requires that each and every element of the claimed invention be disclosed in the prior art. . . . In addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." (see: *Akzo N.V. v. United States International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987).

In addition, "Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, *arranged as in the claim*." See: *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984) (emphasis added).

Finally, "A prior art reference anticipates a claim only if the reference discloses, either expressly or inherently, every limitation of the claim. . . . "'[A]bsence from the reference of any claimed element negates anticipation.'" See: *Row v. Dror*, 42 USPQ 2d 1550, 1553 (Fed. Cir. 1997) (quoting *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81, 84 (Fed. Cir. 1986)).

Claim 1 has now further been amended to clarify that the pilus protein portion is a pilus protein that has been structurally stabilized by addition of a donor strand to complement the pilus protein structure to form a donor strand complemented (dsc) pilus protein attached to an effector, where the latter is not a chaperone or another pilus protein, or any part thereof.

In support, Applicants direct the Examiner's attention to the application at page 6, lines 4-16, and to Figures 3 and 5 and their description on page 11, and to page 16, lines 4-16, and to page 19, line 23, over to page 20, line 2.

The Examiner has noted that no sequences are provided. However, these are all disclosed in a co-pending application (see U.S. Application Serial No. 09/615,846, filed July 13, 2000, specifically incorporated by reference at page 5, line 7-8 of the present application). The specific sequences are not necessarily essential to the present invention because the proteins themselves are well known and the other application discloses the donor strand concept along with common inventorship with the present application.

To summarize the present invention, based on the specification and selecting an adhesin like FimH as the pilus protein, gram negative bacteria are known to use pilus proteins to assemble pili that are tipped with an adhesin (such as FimH or PapG), which process is called the usher-chaperone pathway (see description in application at page 2, lines 8-15). This adhesin contains a domain that binds to mannose, which is present in glycoproteins found on the surface of mammalian epithelial cells, thereby allowing the bacteria to attach to the epithelial cells and initiate an infection (see application at 2, lines 17-23).

Such adhesins are not stable unless they are in a pilus or are bound to a bacterial chaperone (see application at page 17, lines 18-21, for a list of chaperones). In the pilus, an N-terminal segment of a pilus protein inserts into a groove of the adhesin and stabilizes it. In a complex with the chaperone, the G1 domain of the chaperone inserts into the groove of the adhesin and stabilizes it. Applicants have discovered (see U.S. Application Serial No. 09/615,846, referred to above) that only this short strand (N-terminal of certain pilins (such as FimG) or the G1 strand of a chaperone, such as FimC or PapD) is required to stabilize the pilus protein, or adhesin, and keep it in its native

conformation where it has ability to bind to epithelial cells. (see application at page 5, line 10, over to page 6, line 16)

This stabilizing segment may be covalently bound, or otherwise attached, to the pilus protein (especially at the C-terminus of the pilus protein) and is referred to as a donor strand. This forms a donor strand complemented pilus protein. (see application at page 8, lines 8-16, defining the term "donor strand" and at page 34, line 26, to page 35, line 7, defining "donor strand complementation" and "donor strand complemented").

Thus, the present invention provides an isolated protein construct made up of a structurally stabilized pilus protein (i.e., a donor strand complemented pilus protein, or dsc-pilus protein – see application at page 7, lines 7-27, for a list of preferred pilus proteins) attached to an effector, such as an antibody or chemotherapeutic agent, whereby the resulting protein construct serves to direct the effector to specific locations in a mammal where the pilus protein, such as an adhesin, is able to bind, such as urinary tract where bacteria are located, thereby targeting the effector to a particular location.

Uses for the isolated protein construct are described throughout the application, especially at page 37, lines 16-31, where the size of the donor strand is also described, at page 28, line 30, to page 29, line 3, and at page 29, lines 19-24.

In no way does Jones disclose any of this. Jones discloses that a new chaperone, FimC, will bind to FimH and he uses hemagglutination to follow pilus assembly. Pili are assembled on bacteria but claim 1 states that the pilus protein is not attached to a bacterial cell. In addition, hemagglutination does not disclose "antibodies" as stated in the Office Action. Applicants do not see any other reference to immunoglobulins except the statement in the Abstract of Jones that chaperones have an immunoglobulin-like fold. However, they are certainly not immunoglobulins and claim 1 states that no part of a chaperone or pilus protein forms the effector.

As stated in the Lindemann case, cited above, the elements of the claim must be disclosed in the reference and arranged as in the claim. Jones does not disclose any immunoglobulin, or other type of effector, attached to a pilus protein. Jones only discloses hemagglutination in studying pilus assembly but the claim is directed to an isolated protein construct and not to pili being assembled on a bacterial cell.

In sum, Jones does not disclose an isolated protein construct containing a structurally stabilized pilus protein attached to an effector where the latter is not all or part of a chaperone or another pilus protein. Of course, in an assembled pilus, each pilus protein would be attached to another pilus protein.

Applicants also direct the Examiner's attention to the Langermann et al reference (Science, 1997, Examiner's ref. U and Applicants' ref. I1) wherein it is stated that production of large amounts of adhesin as a vaccine is thwarted by the fact that the adhesin is not stable whereas attachment to a chaperone serves to stabilize it. (See Langermann et al at page 607, column 1, last 4 lines, over to top of column 2).

Claims 1-5, 7-9 and 25-32 were rejected under 35 U.S.C. 102(b), as being anticipated by Jones et al (1995).

In response, Applicants reiterate their response as to Jones et al (1993). In addition, Applicants note that Jones (1995) only discloses that they used an anti-FimH antibody and that the basis for the rejection is that this antibody, bound to FimH, would fall within the claim. However, once the antibody is bound to FimH as antibody-antigen complex, the antibody would no longer act as an effector since its antigen binding region would be tied to the FimH.

In addition, amended claim 1 recites that the pilus protein, such as an adhesin, for example, FimH, is a structurally stabilized pilus protein formed of a dsc-pilus protein. This is not disclosed by Jones et al (1995).

Claims 1-19, 25-32 and 53-54 were rejected under 35 U.S.C. 102(b), as being anticipated by Thankavel et al (1997).

In response, Applicants reiterate their earlier responses. In addition, Applicants contend that Thankavel et al does not disclose any type of structurally stabilized pilus protein, especially not a donor strand complemented pilus protein. Thankavel et al only disclose antibodies against specific domains of FimH and the FimH molecule itself, although this is not structurally stabilized, either with a donor strand or otherwise. Thus, Thankavel et al do not anticipate claim 1 with or without amendment thereof.

No fee is believed due in filing this response. The Commissioner is authorized to charge any required fees to Deposit Account No. 03-0678.

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